Of note is that senescent T-cells do not express CD28, but that, on the other hand, not all $CD28^-$ T-cells are senescent.

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The impact of antiretroviral therapy on HIVAN

To the Editor: We read with interest the article by Wei et al [1] on the association between anigotensin-converting enzyme inhibition (ACE-I) and outcomes among patients with human immunodeficiency virus–associated nephropathy (HIVAN). We are concerned about the inherent limitations in making concrete conclusions from observational data and would caution nephrologists against relying too heavily on ACEI, while de-emphasizing the role of antiretroviral therapy (ARV) in the treatment of HIVAN. The authors show that fosinopril, not ARV, is an important predictor of mortality. With the introduction of highly active antiretroviral therapy (HAART), the survival benefit from ARV therapy is indisputable. Failure to show such a benefit raises important questions about the data; specifically, what classes of ARV were available during the course of this study. In the absence of more information in this regard, it is conceivable that the benefits of ACE-I, which decreased the risk of death 100-fold, may be overstated.

The cohort was recruited between 1993–1997 before the availability of HAART, and the current work represents long-term follow-up of the original survivors. Only 16 patients were followed for more than one year, minimally overlapping the contemporary era in which HAART has so significantly improved survival. Most of these patients were treated with ACE-I and were originally coded as not taking ARV. Because most of the deaths occurred within the first year of enrollment, it would not be fair to ascribe long-term benefits of survivors to ACE-I if, in fact, survivors had access to potent ARV, such as HAART, years after they were coded as not having been treated at baseline. Another concern is the observation that the cohort includes 11 patients who survived but were followed for less than one year. All 11 of these patients were taking ARV. Said another way, survivors not taking ARV were followed for 1200 days, while survivors taking ARV were followed for only 385 days. There seems to be considerable nonrandom loss to follow-up in the ARV group, which by itself would skew the data to more favorable outcomes for ACE-I. Bias could also be introduced by factors not included in this analysis, such as perceptions about patient compliance, which could influence the decision to begin antiretroviral therapy or ACE-I, HIV RNA levels, and how CD4 count and HIV RNA levels change over time with ARV. Finally, nonrandom misclassification bias likely impacted the significance of ARV on outcomes. The definition of ARV exposure is $\geq$30 consecutive days. This is not sufficient exposure to derive any meaningful benefit from the drugs, yet patients with minimal exposure could easily have been labeled as having been treated.

Therefore, for these reasons, we do not believe these data can assess the impact of ARV on renal outcomes among patients with HIVAN. Given prior reports which suggest that increasing CD4 lymphocyte counts and nondetectable HIV RNA levels are associated with better renal outcomes [2, 3], and the trend toward greater use of antiretroviral medications in the group receiving fosinopril, we believe that the *real* question not addressed by these data becomes "Does disrupting the renin-angiotensin system affect the progression of HIVAN among patients with effective suppression of viral replication?"

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